

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
10 January 2002 (10.01.2002)

PCT

(10) International Publication Number
WO 02/002638 A3

(51) International Patent Classification²: **A61K 38/17**,
45/06, A61P 19/02, 37/04

(74) Agents: **SHER, Audrey, F.**; Bristol-Myers Squibb Company, P.O. Box 4000, Lawrenceville-Princeton Road, Princeton, NJ 08543-4000 et al. (US).

(21) International Application Number: PCT/US01/21204

(22) International Filing Date: 2 July 2001 (02.07.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/215,913 3 July 2000 (03.07.2000) US

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(71) Applicant (*for all designated States except US*): **BRISTOL-MYERS SQUIBB COMPANY** [US/US]; P.O. Box 4000, Lawrenceville-Princeton Road, Princeton, NJ 08543 (US).

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): **COHEN, Robert** [US/US]; 120 Meadowview Drive, Newton, PA 18940 (US). **CARR, Suzette** [US/US]; 579 Province Line Road, Hopewell, NJ 08525 (US). **HAGERTY, David** [US/US]; 3 Nobadeer Drive, Pennington, NJ 08534 (US). **PEACH, Robert, J.** [NZ/US]; 12848 Via Caballo Rojo, San Diego, CA 92129 (US). **BECKER, Jean-Claude** [FR/US]; 16 Halstead Place, Princeton, NJ 08543 (US).

Published:

— with international search report

(88) Date of publication of the international search report:
30 October 2003

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/002638 A3

(54) Title: METHODS FOR TREATING RHEUMATIC DISEASES USING A SOLUBLE CTLA4 MOLECULE

(57) Abstract: The present invention relates to compositions and methods for treating rheumatic disease by administering to a subject, soluble CTLA4 molecules that block endogenous B7 molecules from binding their ligands.

INTERNATIONAL SEARCH REPORT

Int'l Application No

PCT/US 01/21204

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K38/17 A61K45/06 A61P19/02 A61P37/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, SEQUENCE SEARCH, CHEM ABS Data, MEDLINE, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 968 510 A (LEDBETTER JEFFREY A ET AL) 19 October 1999 (1999-10-19) column 8, line 31 - column 11, line 45 column 34, line 4 - line 14 column 38, line 1 - line 25; table 2 ---	1,3,4, 26,32-34
X	US 5 844 095 A (LEDBETTER JEFFREY A ET AL) 1 December 1998 (1998-12-01) column 4 - column 5 column 11, line 14 - line 45 examples 2,6; table 2 column 9, line 13 - line 30 ---	1,3,4, 26,32-34
E	WO 01 92337 A (SQUIBB BRISTOL MYERS CO ;BAJORATH JURGEN (US); LINSLEY PETER S (US) 6 December 2001 (2001-12-06) the whole document --- -/--	1,3-38

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

17 March 2003

Date of mailing of the international search report

16. 07. 2003

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Bayrak, S

INTERNATIONAL SEARCH REPORT

In Application No
PC 1705 01/21204

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>MORTON P A ET AL: "Differential effects of CTLA-4 substitutions on the binding of human CD80 (B7-1) and CD86 (B7-2 binding of human)" JOURNAL OF IMMUNOLOGY, THE WILLIAMS AND WILKINS CO. BALTIMORE, US, vol. 156, no. 3, 1 February 1996 (1996-02-01), pages 1047-1054, XP002098032 ISSN: 0022-1767 the whole document</p> <p>---</p>	1,3-38
A	<p>PEACH R J ET AL: "COMPLEMENTARITY DETERMINING REGION 1 (CDR1)- AND CDR3-ANALOGOUS REGIONS IN CTLA-4 AND CD28 DETERMINE THE BINDING TO B7-1" JOURNAL OF EXPERIMENTAL MEDICINE, TOKYO, JP, vol. 180, no. 6, 1 December 1994 (1994-12-01), pages 2049-2058, XP000199779 ISSN: 0022-1007 the whole document</p> <p>-----</p>	1,3-38

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 01/21204

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1,3-25, 32-33 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.: 1,3-38 (all partially)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1, 3-38

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1,3-38

Pharmaceutical composition or use of any soluble CTLA4 mutant molecule that binds a B7 molecule, for the therapy of rheumatic diseases, excluding invention 2:

1.1. Claim : 5

Pharmaceutical composition or use of a soluble CTLA4 mutant molecule that binds a B7 molecule (SEQ ID NO 17) having a mutation at position 104, wherein leucine is substituted with any other amino acid, for the therapy of rheumatic diseases.

1.2. Claim : 6

Pharmaceutical composition or use of a soluble CTLA4Ig mutant (1 through 357; SEQ ID NO 7) that binds a B7 molecule with a mutation at position 104, wherein leucine is substituted with glutamic acid, for the therapy of rheumatic diseases.

1.3. Claim : 7

Pharmaceutical composition or use of a soluble CTLA4Ig mutant (-1 through 357) (SEQ ID NO 7) that binds a B7 molecule with a mutation at position 104, wherein leucine is substituted with glutamic acid, for the therapy of rheumatic diseases.

1.4. Claims: 8, 13,17-25,27-30,32-33,35-38 (all partially)

Pharmaceutical composition or use of soluble CTLA4 mutant molecules (SEQ ID NO 17) that bind a B7 molecule having a double mutations at positions: a) L104EA29X (claims 8, 13,17-25,27-30,32-33,35-38 (all partially)); b) L104EG105X (claims 8 partially); c) L104ES25 (claims 8 partially); d) L104ET30X (claims 8 partially), for the therapy of rheumatic diseases.

1.5. Claims: 9,11,14,28,36(all partially), and15, 29,37

Pharmaceutical composition or use of a soluble CTLA4Ig mutant (1 through 357; SEQ ID NO 9) that binds a B7 molecule with a mutation at positions 104 (leucine is substituted with glutamic acid), and 29 (alanine is substituted by tyrosine), for the therapy of rheumatic diseases.

1.6. Claim : 9 (partially)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Pharmaceutical composition or use of a soluble CTLA4Ig mutant (1 through 357; SEQ ID NO 11) that binds a B7 molecule with a mutation at positions 104 (leucine is substituted with glutamic acid), and 29 (alanine is substituted by leucine), for the therapy of rheumatic diseases.

1.7. Claim : 9 (partially)

Pharmaceutical composition or use of a soluble CTLA4Ig mutant (1 through 357; SEQ ID NO 13) that binds a B7 molecule with a mutation at positions 104 (leucine is substituted with glutamic acid), and 29 (alanine is substituted by threonine), for the therapy of rheumatic diseases.

1.8. Claim : 9 (partially)

Pharmaceutical composition or use of a soluble CTLA4Ig mutant (1 through 357; SEQ ID NO 15) that binds a B7 molecule with a mutation at positions 104 (leucine is substituted with glutamic acid), and 29 (alanine is substituted by tryptophan), for the therapy of rheumatic diseases.

1.9. Claims: 10,16,30,38, and partially 11,14,28,36

Pharmaceutical composition or use of a soluble CTLA4Ig mutant (-1 through 357; SEQ ID NO 9) that binds a B7 molecule with a mutation at positions 104 (leucine is substituted with glutamic acid), and 29 (alanine is substituted by tyrosine), for the therapy of rheumatic diseases.

1.10. Claim : 10

Pharmaceutical composition or use of a soluble CTLA4Ig mutant (-1 through 357; SEQ ID NO 11) that binds a B7 molecule with a mutation at positions 104 (leucine is substituted with glutamic acid), and 29 (alanine is substituted by leucine), for the therapy of rheumatic diseases.

1.11. Claim : 10

Pharmaceutical composition or use of a soluble CTLA4Ig mutant (-1 through 357) (SEQ ID NO 13) that binds a B7 molecule with a mutation at positions 104 (leucine is substituted with glutamic acid), and 29 (alanine is substituted by threonine) for the therapy of rheumatic diseases.

1.12. Claim : 10

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Pharmaceutical composition or use of a soluble CTLA4Ig mutant (-1 through 357; SEQ ID NO 15) that binds a B7 molecule with a mutation at positions 104 (leucine is substituted with glutamic acid), and 29 (alanine is substituted by tryptophan), for the therapy of rheumatic diseases.

1.13. Claim : 12

Pharmaceutical composition or use of a soluble CTLA4 mutant molecules (SEQ ID NO 17) that binds a B7 molecule having a first mutation at position 104 (L to E), a second mutation at positions 29 (A to Y), and a third mutation at position 25 (any other amino acid), for the therapy of rheumatic diseases.

1.14. Claims: 13, and partially 17-25,27-30,32-33,35-38

Pharmaceutical composition or use of a soluble CTLA4 binds a B7mutant molecules (SEQ ID NO 17) that molecule having a mutation at position 104 (L to E), and a second mutation at positions 29 (A to Y) for the therapy of rheumatic diseases.

2. Claims: 2,39

Pharmaceutical composition or use of any soluble CTLA4 mutant molecules that binds a B7 molecule further having an immuno suppressive agent, for the therapy of rheumatic diseases.

Please note that all inventions mentioned under item 1, although not necessarily linked by a common inventive concept, could be searched without effort justifying an additional fee.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1,3-38 (all partially)

1. Present claims 1,3-5,8,12,13,17-27,31-34 relate to an extremely large number of possible compounds, namely "soluble CTLA4 mutants", or "soluble CTLA4 mutant molecule comprises a mutation...". Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.

2. Claims 1,3-16,18-38 relate to the use of a pharmaceutical preparation for prophylaxis or treatment of "rheumatic diseases", which encompasses a multitude of different diseases. The claims thus cover a rather large number of diseases, whereas the application provides support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT for only a very limited number of diseases. Consequently, the claims lack support and the application lacks disclosure. Independent of the above reasoning, the claims 1,3-16,18-38 also lack clarity because it is not fully possible to determine the diseases for which protection might legitimately be sought (Article 6 PCT).

3. Claim 18 is related to the prevention or treatment of diseases which are not clearly defined, namely conditions related to "alleviating a symptom associated with a rheumatic disease selected...". Due to the functional definition of the claimed subject-matter, the scope of protection of the claim 18 is obscure and not limited to the treatment of said specified conditions in the description and/or the claims but, by contrast, embraces an undefined number of other conditions allegedly capable of being improved or prevented by the administration of soluble CTLA4 mutants. Therefore, the claim 18 lacks support (Article 6 PCT) and the application lacks disclosure (Article 5 PCT). Independent of the above reasoning the terms such as "structural damage", "pain", and "elevated level of..." are vague and unclear and leave the reader in doubt as to the meaning of the technical feature to which they refer, thereby rendering the definition of the subject-matter of claim 18 unclear (Article 6 PCT).

Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the use of the specific mutants as mentioned in claims 6,7,9,10,14,15 in the treatment of rheumatoid arthritis; and with due regard to the general concept of the invention, i.e. CTLA4 molecules having mutations at positions 25,29,30,104, or 105, and which may be embedded within a sequence.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Int. Application No

PCT/US 01/21204

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5968510	A	19-10-1999	US 5885796 A 23-03-1999
			US 5844095 A 01-12-1998
			US 6090914 A 18-07-2000
			US 5770197 A 23-06-1998
			US 5851795 A 22-12-1998
			US 5977318 A 02-11-1999
			US 5885579 A 23-03-1999
			AU 701310 B2 28-01-1999
			AU 1645895 A 26-10-1995
			CA 2146895 A1 16-10-1995
			EP 0682039 A1 15-11-1995
			FI 951801 A 16-10-1995
			JP 8047391 A 20-02-1996
			NO 951436 A 16-10-1995
			US 5773253 A 30-06-1998
			AU 682325 B2 02-10-1997
			AU 5390194 A 28-07-1994
			CA 2113744 A1 23-07-1994
			EP 0613944 A2 07-09-1994
			FI 940270 A 23-07-1994
			IL 108374 A 29-02-2000
			JP 7069914 A 14-03-1995
			NO 940228 A 25-07-1994
			AT 170562 T 15-09-1998
			AU 661854 B2 10-08-1995
			AU 2240092 A 25-01-1993
			CA 2110518 A1 07-01-1993
			DE 69226871 D1 08-10-1998
			DE 69226871 T2 12-05-1999
			DK 606217 T3 09-11-1998
			EP 0606217 A1 20-07-1994
			ES 2123001 T3 01-01-1999
			FI 935795 A 22-12-1993
			FI 20022285 A 30-12-2002
			IE 922111 A1 30-12-1992
			JP 6508989 T 13-10-1994
			JP 2002017349 A 22-01-2002
			JP 2002003399 A 09-01-2002
			JP 2003012546 A 15-01-2003
			JP 2003096097 A 03-04-2003
			KR 238712 B1 15-01-2000
			MX 9203605 A1 01-11-1993
			NO 934801 A 21-02-1994
			NO 20020491 A 21-02-1994
			NZ 243286 A 26-03-1996
			NZ 264712 A 26-03-1996
			PT 100637 A ,B 31-05-1994
US 5844095	A	01-12-1998	US 6090914 A 18-07-2000
			US 5770197 A 23-06-1998
			US 5851795 A 22-12-1998
			US 5885796 A 23-03-1999
			US 5977318 A 02-11-1999
			US 5968510 A 19-10-1999
			US 5885579 A 23-03-1999
			AU 701310 B2 28-01-1999
			AU 1645895 A 26-10-1995
			CA 2146895 A1 16-10-1995

INTERNATIONAL SEARCH REPORT

Int. Application No

PCT/US 01/21204

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5844095	A	EP 0682039 A1	15-11-1995
		FI 951801 A	16-10-1995
		JP 8047391 A	20-02-1996
		NO 951436 A	16-10-1995
		US 5773253 A	30-06-1998
		AU 682325 B2	02-10-1997
		AU 5390194 A	28-07-1994
		CA 2113744 A1	23-07-1994
		EP 0613944 A2	07-09-1994
		FI 940270 A	23-07-1994
		IL 108374 A	29-02-2000
		JP 7069914 A	14-03-1995
		NO 940228 A	25-07-1994
		AT 170562 T	15-09-1998
		AU 661854 B2	10-08-1995
		AU 2240092 A	25-01-1993
		CA 2110518 A1	07-01-1993
		DE 69226871 D1	08-10-1998
		DE 69226871 T2	12-05-1999
		DK 606217 T3	09-11-1998
		EP 0606217 A1	20-07-1994
		ES 2123001 T3	01-01-1999
		FI 935795 A	22-12-1993
		FI 20022285 A	30-12-2002
		IE 922111 A1	30-12-1992
		JP 6508989 T	13-10-1994
		JP 2002017349 A	22-01-2002
		JP 2002003399 A	09-01-2002
		JP 2003012546 A	15-01-2003
		JP 2003096097 A	03-04-2003
		KR 238712 B1	15-01-2000
		MX 9203605 A1	01-11-1993
		NO 934801 A	21-02-1994
		NO 20020491 A	21-02-1994
		NZ 243286 A	26-03-1996
		NZ 264712 A	26-03-1996
		PT 100637 A ,B	31-05-1994
WO 0192337	A	06-12-2001	
		AU 6346601 A	11-12-2001
		CA 2409748 A1	06-12-2001
		EP 1248802 A2	16-10-2002
		NO 20025656 A	25-11-2002
		WO 0192337 A2	06-12-2001
		US 2002182211 A1	05-12-2002